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COMPARISON OF TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND OIL OF EVENING PRIMROSE IN MANAGEMENT OF MASTALGIAS; A RANDOMIZED CONTROLLED TRIAL.

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ABSTRACT… Objectives: To compare the effects of topical non-steroidal anti-inflammatory drugs over oil of evening primrose in mastalgias in terms of frequency of pain. **Study Design:** Randomized Controlled Trail. **Setting:** Department of Surgical at Holy Family Hospital, Rawalpindi. **Period:** January 2016 to June 2016. **Material & Methods:** A total of 160 consecutive female patients, ages 17-45 years with history of breast pain for last 2-3 months (cyclic and noncyclic), were presenting in surgical OPD with symptoms of mastalgias between January 2016 to June 2016 included in the study. Patients allocated in two groups, Group A received topical NSAID in 0.5% Piroxicam gel for local application to affected area twice daily for three months and Group B was given oil of evening primrose (OEP) capsules (Efamol) 500mg twice daily for three months. Patients mastalgia pain was recorded by using VAS scale at baseline (1st day) and at end of treatment (3rd month). Pain calculated by compared in terms of mean, standard deviation between groups and independent sample T test was used. Percentage compare the efficacy of response of two therapies among group A and group B chi-square distribution was used. **Results:** One hundred and sixty (160) patients were recruited in this study. The mean ages of the patients were 27.54±7.53 years with minimum 17 and maximum 45 years. Out of 160 patients, 115 (71.9%) were younger than 30 years of age and 45 (28.1%) were between 30 and 45 years of age. Results showed significantly lower pain in patients using topical NSAIDs as compared to OEP capsules (p=0.001). **Conclusion:** Topical NSAIDs are more significant and show more improvement in reduction of pain in both cyclic and noncyclic mastalgia patients as compared to oil of evening primrose.

Key words: Breast, Evening Primrose Oil, Non-Steroidal Anti-Inflammatory Agents, Pain.

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INTRODUCTION

Mastalgia (breast pain) is one of the commonest symptoms for which women present to general surgical OPD and a cause of anxiety among female patients as well.[1] 47% of patients visiting general surgical outpatient departments for breast related problems have mastalgia as the underlying cause.[2] As the awareness and health education is increasing amongst the people all over the world, more people including the females seek medical advice regarding their health status and diseases. Half of the world comprises of females. In Pakistan more than 30% are women between the age of 14-45 years.[3] Although only 5-7% of patients with breast carcinoma presented with mastalgia.[1,2]

Different modalities used for treatment of breast pain include physical measures like wearing of a well fitted bra, a decrease in dietary fat intake, discontinuance of oral contraceptive drugs and hormone replacement agents, nutritional supplements, oil of evening primrose, non-steroidal anti-inflammatory drugs oral as well as topical and a variety of hormonal agents like danazol, tamoxifen or bromocriptine etc.[4] The most commonly used pharmacological treatment includes either nsaids or oil of evening primrose.[1] Some 77% of patients treated can obtain useful relief from their symptoms.[5] Evening primrose oil has been widely used in west as a first line therapeutic option with danazol and bromocriptine as second line therapy.[4] In various

studies danazol was found to be most effective drug with 70% efficacy while bromocriptine and oil of evening primrose have equal efficacy 45-47%. In another study tamoxifen was found to be most effective and least toxic hormonal agent for treatment of chronic refractory mastalgia. Although hormonal agents are more effective in treating both cyclic and non-cyclic mastalgias, they are associated with serious side effects making them unacceptable to most women.[4] Surprisingly, limited studies have been done for role of oral as well as topical non-steroidal anti-inflammatory drugs for treatment of breast pain. A randomized study of topical non-steroidal anti-inflammatory drugs showed significant reduction (81%) in breast pain with no side effects. On the other hand another study demonstrated that topical non-steroidal anti-inflammatory drugs had no beneficial effect in managing mastalgia.[4] Therefore the overall picture remains blurred. In our country one such study that was carried out in Karachi by S. Qureshi et al[1] showed that 64% of patients treated with oil of evening primrose had a clinically significant response after three months of treatment, compared with 92% with topical non-steroidal anti-inflammatory drugs.

The rationale of this study was comparing the NSAIDs with evening primrose oil and their efficacy in the treatment of both cyclic and noncyclic mastalgias. And these agents have less systemic side effects so the patient's compliance was improved. These agents are not frequently used in our setup. So this study provided us with fresh evidence about reduction of pain by using these agents. It was decided to disseminate the results to the general surgeons and recommend the routine use of topical non-steroidal anti-inflammatory agents in mastalgia patients if the pain is equal or less than evening primrose oil.

MATERIAL & METHODS

After approval from ethical committee of the hospital, this randomized controlled trail was carried out in Surgical Department of Holy Family Hospital (HFH) from January 2016 to June 2016. After informed written consent a total of 160 patients (sample size calculated by using, level of significance=5%, power of test=80%, two population proportions=64% and 92%)[1] with history of breast pain for last 2-3months (cyclic and noncyclic) and age 17 to 45 years presenting in OPD were examined by clinician with 02 years' experience. Patients presenting with diabetes, breast malignancy, a discrete lump, nipple discharge, lactation and obvious breast abscess, patients taking oral contraceptives, post-menopausal women were excluded from study. Patients refusing informed consent were also excluded from study. Ultrasonography of the breast and mammography, were used to differentiate between benign breast diseases and occult carcinoma, especially where there was a positive family history for breast cancer. 80 Patients were randomly allocated to group A (Topical NSAIDs) and 80 to group B (Oral OEP capsules) by non-probability consecutive sampling. Two groups were made by the help of lottery method.

The following procedure was done for evaluation of the patients; visual analogue scale and breast pain chart was filled to monitor pain response. At baseline (1st day) and at the end of treatment breast pain chart was measured and the score of VAS was calculated. Patients in group A received topical NSAIDs 0.5% Piroxicam gel for local application to affected area twice daily for three months and group B received oral OEP capsules (Efamol) 500mg twice daily for three months. Each patient had undergone a thorough history and a detailed physical examination was carriedout. Pain was recorded in both groups by using visual analogue scale VAS at end of treatment.

Data analysis was done by SPSS-20. Quantitative variable pain was calculated in terms of mean and standard deviation. Frequency and percentages were calculated for ages, pain and efficacy between two agents. Mean pain score at baseline and at end of treatment between two groups was compared by using independent sample T test keeping p value ≤ 0.05 as significant. Percentage compare the efficacy of response of two therapies among Group A and Group B, chi-square was used.

RESULTS

A total of 160 patients (80 in each group) were

evaluated for mastalgia. Mean age of the patients was 27.54±7.53. Out of 160 patients 115 patients (71.9%) were younger than 30 years of age and 45 (28.1%) were between 30 and 45 years of age. Out of 160 patients 110 patients (68.75%) were cyclic mastalgia and 50 (31.25%) were noncyclic mastalgia. Out of 160 patients 60 (37.5%) had mild to moderate pain, 98 (61.25%) had moderate pain and 2 (1.25%) had severe pain.

The results showed that 95% of patients in group A responded to treatment (p=0.001), which was statistically significant. NSAIDS showed a better response than oil of evening primrose, with 95% of patients responding at three months in comparison to 68.8% with oil of evening primrose.

DISCUSSION

Mastalgia or mastodynia, clinically taken to be breast pain without any underlying pathology[6], is a common condition affecting up to 70%, of women at some point in their lives and was known to medical practitioners much earlier.[7]

The results of this study showed that overall efficacy of both drugs showed that topical NSAIDs are highly effective (LOS=0.05) in comparison with oil of evening primrose. NSAIDS showed a better response than oil of evening primrose, with 95% of patients responding at three months in comparison to 68.8% with oil of evening primrose.

According to literature females usually report mild breast pain for 2-3 days, and almost 8-30% of females had reported moderate to severe pain which lasts for 5 or more days in a month[7] which is comparable with the mean pain index of chronic cancer.[8] So, 15% of Females presenting in breast clinics needed medication.[9]

Preece et al[10] had stated that there is no relationship between mastalgia and total body water, showing that water restriction has no role in mastalgia, so there is no use of restricting sodium or using diuretics. A study[11] had examined morphological structures of 335 females in Germany using ultrasound out of which 212 had breast pain.

There was a positive co relation between width of milk ducts, duct ectasia and mastalgia, especially in noncyclic mastalgia. According to a study statistics[12], around 75-85% of patients require no treatment and reassurance alone is sufficient, however those women in whom pain remains constant and interferes with their routine activities including sleep and emotional disturbances need treatment of some sort.

		Group A		Group B	
		Frequency	Percent	Frequency	Percent
Valid	Decrease of 2 units	10	12.5	36	45.0
	Decrease of 3 units	52	65.0	19	23.8
	Decrease of 4 units	14	17.5	3	3.8
	No response	4	5.0	22	27.5
	Total	80	100.0	80	100.0

Table-I. Breast pain chart between two group, N=160.
The likelihood of superiority (LOS), α = 0.05 between two groups.

	Paired Differences				
	Mean	Std. D	Std. Error	df	Sig. (2-tailed)
Pair 1 group A – group B	1.63	0.17	.097	79	.012

Table-II. VAS pain score between groups, N = 160

Efficacy	Yes		No		P-Value
	Frequency	Percent	Frequency	Percent	
Group A	76	95	4	5	.001
Group B	55	68.8	25	31.3	

Table-III. Efficacy of NSAIDs and OEP between groups, N = 160.

Various treatment modalities are currently in use for management of breast pain including psychological assessment and support because according to SOGC guidelines education and reassurance is an integral part of management of mastalgia and should be the first line of treatment according to several studies (evidence level II-1A).[6] Use of caffeine has also been implicated as a causative factor and two observational studies have also been done by Minton[13,14] in which resolution of signs and symptoms occurred in 85% of women who abstained from methylxanthines for a period of 8 weeks or more, but according to level 1-E evidence provided by SOGC guidelines, women with breast pain should not be advised to reduce caffeine intake. Hormonal preparations are also used for treatment of mastalgias, but according to a multi institutional cross section study[15], it is still unclear whether oral contraceptives cause or relieve mastalgia. Several other treatments that are used include vitamin E, vitamin B6, phytoestrogens and herbs including ginseng and chasteberry. The medications used include progesterone cream, topical NSAIDs, tamoxifen, danazol, bromocriptine, oil of evening primrose and as a last resort surgery has also been tried for relief of mastalgia, although the experience is very limited. Davies et al[16] had determined that surgery would only be indicated only if all other conservative treatments failed in certain females and all the complications along with the possibility of pain(50% cases) should be reported to the patients.

So, in a nutshell, the overall picture for a definitive management plan for mastalgia depends on patient compliance and the cause of mastalgia and in this study we evaluated the efficacy of two most commonly used drugs for mastalgia, that were topical NSAIDs and oil of evening primrose, which can be found near mountains, streams, roadsides and so is a natural product rather than a drug rich in essential fatty acids like linolenic acid. Our body converts linolenic acid into a hormone like substance prostaglandin, particularly PGE-1[17] that helps in reduction of inflammatory cells.

The limiting factor being that this study has been carried out for a period of 3 months only, and result evaluation was done at end of three months, so it remains to be determined whether this response was maintained or not and if so, then for how long. Overall the results show that topical NSAIDS significantly reduces pain as compared to oil of evening primrose.

CONCLUSION

The study concluded that mean topical NSAIDs being an effective mode of treatment for both cyclic and noncyclic mastalgia after three months of therapy.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
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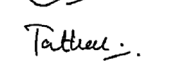
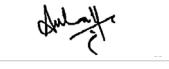
2	Ahmed Raza	Participation in active methodology, Assembly of data, Statistical expertise.	
3	Tahira Hameed	Critical revision of the article for important intellectual content.	
4	Naveed Arshad	Analysis and interpretation of the data and drafting.	
5	Syed Tatheer Abbas	Participation in statistical analysis and discussion.	
6	Arrham Hai	Active participation in discussion.	